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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/768,012	01/22/2001	Michael J. McCluskie	C1040/7010	9273

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 08/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/768,012	MCCLUSKIE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10,11,16-31,52 and 102-111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10,11,16-31,52 and 102-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/11/05;3/28/05*; 2/25/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SDO

DETAILED ACTION

This application has been transferred to examiner Quang Nguyen, Ph.D. in GAU 1633.

Applicant's amendment filed on 5/18/05 has been entered.

Amended claims 1-6, 10-11, 16-31, 52 and 102-111 are pending in the present application, and they are examined on the merits herein.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 10-11, 16-31, 52 and 102-111 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons already set forth in the Office Action mailed on 12/15/04 (pages 3-5).

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 5/18/05 (pages 7-9) have been fully considered, but they are not found persuasive.

1. Applicants argue mainly that that the structure of a nucleic acid is known in the art, and the induction of a Th2-biased immune response is independent of the sequence of the nucleic acid apart from the Th1 immunostimulatory motifs (e.g., CpG dinucleotides, poly T motifs and poly G motifs) that are specifically excluded.

Although the structure of a nucleic acid is known in the art, the structure(s) or element(s) that is essential or responsible for the induction of a Th2-biased immune response in a subject is unknown. Unlike the well characterized Th1 immunostimulatory motifs, apart from the disclosed SEQ ID NO:1 or SEQ ID NO:2 the instant specification fails to describe any other sequences or essential motifs that are critical for the induction of a Th2-immune response in *in vivo*. Even with SEQ ID NO:1, there is no evidence of record indicating that the oligonucleotide is capable of inducing a Th2-biased immune response in a subject by any route of delivery other than the mucosal administration (e.g., dermal or parenteral administrations). On the contrary, the specification teaches specifically that no augmentation of antigen-specific IgG was seen with the ODN 1986 having SEQ ID NO:1 when it is co-administered with either HbsAg or influenza virus vaccine intramuscularly at the oligonucleotide dosages of 10ug and 50ug, respectively (see Figures 2 and 5). There is also no evidence of record indicating that the induced Th2-biased immune response *in vivo* is independent of sequence of the nucleic acid that is absent of Th1 immunostimulatory motifs as asserted by

Applicants. Nor does the present disclosure teach a representative number of species for a broad genus Th2-immunostimulatory nucleic acid to be used in the methods as claimed.

2. With respect to the cited reference of Zhao et al, Applicants argue that their findings are not consistent with the claimed invention because the reference reported that an oligonucleotide lacking a CG dinucleotide failed to induce a Th1 cytokine, and it said nothing of the ability of such oligonucleotide to stimulate a Th2 immune response.

It is noted that neither the prior art nor the instant specification disclose the non-CG oligonucleotide of Zhao et al. or any other non CpG oligonucleotide apart from SEQ ID NO:1 that is capable of inducing a Th2-biased immune response *in vivo* under any conditions.

Since the instant specification fails to identify relevant structural characteristics that are correlated to the induction of a Th2-biased immune response *in vivo*, coupled with the lack of disclosure for a representative number of species for a broad genus of Th2-immunostimulatory nucleic acids to be used in the methods as claimed, the skilled artisan would not conclude that Applicants had possession of the claimed invention.

Claims 1-6, 10-11, 16-31, 52 and 102-111 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of mucosally administering a Th2-immunostimulatory nucleic acid comprising SEQ ID NO:1 or SEQ ID NO:2 in combination with an antigen to a subject, does not reasonably provide enablement for a method for inducing a Th2-biased antigen specific immune response

in a subject by administering any other Th2-immunostimulatory nucleic acids or by a non-mucous administration of any Th2-immunostimulatory nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons already set forth in the Office Action mailed on 12/15/04 (pages 6-12).

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 5/18/05 (pages 7-9) have been fully considered, but they are not found persuasive.

Applicants argue mainly that the Examiner has failed to meet his burden regarding a *prima facie* case of lack of enablement and that the references cited by the Examiner of the state of the art are not inconsistent with the claimed invention. For examples, with respect to the article of McCluskie et al. (Vaccine 19:413, 2001) on the issue that immunostimulation by non-CG containing oligonucleotide was "totally unexpected since non CpG ODN do not have such an effect when delivered by a parenteral route", Applicants argue that parenteral administration of Th2 immunostimulatory oligonucleotides at low doses does not result in Th2 immune stimulation, and higher doses are necessary. With respect to the article of McCluskie et al. (Vaccine 19:2657, 2001) Applicants argue that the data show that two non-CG containing oligonucleotides are Th2 immunostimulatory. With respect to the article of McCluskie et al. (J. Immmunology 161:4463, 1998) on the issue that non-CG

oligonucleotides stimulated no or very low levels of anti-HBs IgG antibodies and no significant levels of fecal IgA, Applicants argue that their findings are not consistent with the claimed invention because the oligonucleotide and antigen doses reported by McCluskie et al. were lower than those used in the instant specification.

1. With respect to Applicant's argument that the Examiner failed to meet his burden regarding a *prima facie* case of lack of enablement, please refer to the detailed analysis of the Wands factors as set forth in the Office Action mailed on 12/15/04 (pages 6-12).

2. With respect to the specific articles cited above, it is noted that none of the references teaches or suggests that any non-CpG containing oligonucleotide is capable of inducing a Th2-biased immune response in a subject by any non-mucosal administration (This is consistent with the given enabled scope). Moreover, the specification teaches specifically that no augmentation of antigen-specific IgG was seen with the ODN 1986 having SEQ ID NO:1 when it is co-administered with either HbsAg or influenza virus vaccine intramuscularly at the oligonucleotide dosages of 10ug and 50ug, respectively (see Figures 2 and 5). Applicants have not provided any objective evidence other than personal opinions that higher doses of non-CpG oligonucleotides would elicit Th2-biased immune responses in a subject through a parenteral route of administration, despite the specific teachings in Figures 2 and 5 of the present application. Due to the lack of sufficient guidance provided by the instant specification on the relevant structural characteristics that are correlated to the induction of a Th2-biased immune response *in vivo*, coupled with the state of the prior art at the effective

filing date of the present application, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed with a broad genus of Th2-immunostimulatory nucleic acids. Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> *That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.*

Accordingly, claims 1-6, 10-11, 16-31, 52 and 102-111 are rejected under 35 U.S.C. 112, first paragraph, for the same reasons already set forth in the Office Action mailed on 12/15/04 (pages 6-12).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

New claim 111 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Claim 111 is vague and indefinite in that the metes and bounds of the term "derived from" are unclear. It is unclear the nature and the number of steps required to obtain a "derivative" of a parasitic antigen. The term implies a number of different steps

that may or may not result in a change in the functional characteristics of a parasitic antigen from the source that it is "derived from". It would be remedial to amend the claim language to use the term "obtained from", which implies a more direct method of acquiring the parasitic antigen.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER